

In The Claims

1. (Twice Amended) A structure comprising a biological membrane adhered with a high resistance seal to a porous or perforated substrate for use in a high throughput screening process, wherein said substrate has pores of diameters between 0.5 μ m and 10 μ m, and wherein the biological membrane comprises an ion channel or transporter and said substrate is disposed between said membrane and a solution perfusion channel.

2. (Thrice Amended) A structure comprising a biological membrane adhered with a high resistance seal to a porous or perforated substrate for use in a high throughput screening process, said substrate having pores of diameters between 0.5 μ m and 10 μ m, and wherein the biological membrane comprises an ion channel or transporter and said substrate is disposed between said membrane and a solution perfusion channel, wherein the biological membrane comprises a contiguous layer of cells which is capable of adhering to a substrate with a high resistance seal wherein each cell forms a tight junction with adjacent cells and expresses an ion channel or transporter which is localized in the cell membrane.

3. (Previously Amended) A structure according to claim 1 or 2 which comprises cells having an ion channel or transporter which naturally resides in the cell membrane thereof or, is insertable by transfection with cDNA and/or cRNA encoding the ion channel or transporter.

4. (Previously Amended) A structure according to claim 1 which comprises a plurality of ions channels or transporters which are predominantly preselected ion channels or transporters of interest.

5. (Previously Amended) A structure according to claim 1 which comprises genetically engineered cells which have been engineered to predominantly express an ion channel or transporter.

6. (Previously Amended) A structure according to claim 1 which comprises voltage gated ion channels.

7. (Previously Amended) A structure according to claim 2 wherein the cells are selected from the group which comprises HEK-293 cells, genetically modified Chinese hamster ovary (CHO) cells, primary neuronal tissue such as hippocampus, dorsal root ganglia, superior cervical ganglia etc.; skeletal muscle; smooth muscle; cardiac muscle; immune cells; epithelia; endothelia.

8. (Previously Amended) A structure according to claim 1 which comprises an ion channel having rapid activation and inactivation kinetics.

9. (Previously Amended) A structure according to claim 1 having an ion channel which shows specificity for an ion selected from the group which comprises sodium, potassium, calcium, chloride.

10. (Previously Amended) A structure according to claim 2 wherein the contiguous layer of cells comprises cells capable of adhering with a high resistance seal to a substrate selected from the group which comprises glass, plastics, rubber, polytetrafluoroethylene (PTFE), PTFE/glass fabric and polyethylene terephthalate (PETP).

11. (Previously Amended) A structure according to claim 1 which comprises a pseudoepithelium wherein one face of a contiguous layer of cells is permeabilized thereby providing access to the interior of the cells.

12. (Original) A structure according to claim 11 which comprises a pseudo-epithelium wherein one face of the contiguous layer of cells is permeabilized by an antibiotic selected from the group which comprises amphotericin an nystatin; or detergent selected from the group which comprises digitonin and saponin; or physical disruption using a high voltage field; or by enzymatic digestion of a part of the membrane using an appropriate enzyme.

13. (Previously Amended) A structure according to claim 1 wherein the substrate is perforated.

14. (Previously Amended) A structure according to claim 1 which comprises a perforated coverslip.
15. (Canceled)
16. (Currently Amended) A structure according to claim 1[5] wherein the pores are of diameter between 1 μ m and 7 μ m.
17. (Currently Amended) A structure according to claim 1[5] or 16 wherein the pores are of diameter 1-2 μ m.
18. (Previously Amended) A structure according to claim 1 which comprises a coverslip having a grid of pores.
19. (Previously Amended) A structure according to claim 1 which comprises a perforated substrate which is manufactured of a material selected from the group which comprises glass, plastics, rubber, polytetrafluorotethylene (PTFE), PTFE/glass fabric and polyethylene terephthalate (PETP).
20. (Previously Canceled)
21. (Previously Canceled)
22. (Currently Amended) A high throughput screen for detecting and assaying compounds with activity on voltage gated ions channels which comprises a biological membrane adhered with a high resistance seal to a porous or perforated substrate for use in a high throughput screening process, said substrate having pores of diameters between 0.5 μ m and 10 μ m, and wherein the biological membrane comprises an ion channel or transporter and said substrate is disposed between said membrane and a solution perfusion channel.

23-28. (Previously Canceled)

29-46. (Previously Canceled)

47. (Previously presented and Allowed) A high throughput screen for detecting and assaying compounds with activity in gated ion channels, comprising:

a wall defining a well with a bottom;

a porous substrate disposed in the well and spaced from the bottom to define a solution perfusion channel between the well bottom and substrate, said substrate being configured to permit adherence of a biological membrane thereto with a high resistance seal;

a first electrode in the well in electrical communication with a bottom side of the substrate; and

a second electrode disposed in the well in electrical communication with a topside of the substrate, said electrodes being configured for electrical measurements through a membrane disposed on the substrate.

48. (Previously presented and Allowed) The high throughput screen of claim 47, wherein said porous substrate comprises a single pore.

49. (Previously presented and Allowed) The high throughput screen of claim 47, wherein said porous substrate comprises a plurality of pores.

50. (Previously presented and Allowed) The high throughput screen of claim 47, wherein said electrodes are connected to a voltage-clamp amplifier.

51. (Previously presented) and Allowed The high throughput screen of claim 47, wherein said first and second electrodes are disposed above the substrate and a seal surrounds the second electrode to insulate it from the first electrode.

52. (Previously presented and Allowed) The high throughput screen of claim 51, wherein said seal comprises an o-ring.

53. (Previously presented and Allowed) The high throughput screen of claim 47, wherein the first electrode is disposed in the bottom of the well and the second electrode is disposed above the substrate.

54. (Previously presented and Allowed) The high throughput screen of claim 47 wherein:

said wall defines multiple wells in a multiwell plate;

said first electrode comprises a plurality of reference electrodes, one each associated with each well; and

said second electrode comprises a recording head comprising at least one recording electrode.

55. (Previously presented and Allowed) The high throughput screen of claim 54, wherein said recording electrode is moveable between wells of the multiwell plate.

56. (Previously presented and Allowed) A high throughput screen for detecting and assaying compounds with activity in gated ion channels, comprising:

a wall defining a well;

a first electrode in a bottom of the well;

a porous substrate disposed in the well and spaced from the first electrode to define a solution perfusion channel there between, said substrate being configured to permit adherence of a biological membrane thereto with a high resistance seal;

a second electrode above the porous substrate;

a voltage-clamp amplifier connected between said electrodes.